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EXAMINER	
SNYDER, STUART	
ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,448	DREVET ET AL.	
	Examiner	Art Unit	
	STUART W. SNYDER	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-66* is/are pending in the application.

4a) Of the above claim(s) *59-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/8/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Printout from NCIB--P04608*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 35-58) in the reply filed on 11/7/2009 is acknowledged. The traversal is on the ground(s) that the special technical feature, stabilized Tat antigen as anti-HIV vaccine, is novel and non obvious in view of Marasco, *et al.* because the cited non-patent literature relates to anti-retroviral gene therapy for treatment of HIV infection and AIDS. Applicants contend that the gene therapeutic strategy is different from Applicants' anti-HIV vaccine strategy and furthermore that the special technical feature is stabilized tat antigen with respect to proteolytic degradation. This is not found persuasive because the stabilized tat antigen taught by Marasco, *et al.* inherently possesses the required property, e.g., resistance to proteolytic degradation. It is well known in the protein chemistry arts that antibodies mask protein sites potentially susceptible to proteolytic cleavage. This is seen even *in vivo* in the work of Xian, *et al.* wherein IGF-1 was protected from proteolytic cleavage by complexing the growth factor with antibodies; the half-life of IGF-1 in the gastrointestinal track was increased approximately 28 fold. In a similar manner, the “intrabodies” produced in transfected cells by Marasco, *et al.* inherently protect tat in the same cells from intracellular proteases. Thus, Marasco, *et al.* teaches “stabilized Tat antigen resistant to proteolytic cleavage".

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 59-66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/7/2008.

3. Applicant is reminded that in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 35-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to a HIV vaccine composition. Although intended use of a composition does not necessarily impose structural constraints on a composition, the intended use of the composition of the instant application imposes functional constraints on the composition. Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)).

Nature of the invention. The instant invention is drawn to a vaccine for HIV. The term "vaccine," by definition, implies a preparation intended for active immunological prophylaxis. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease.

State of the prior art. It is well known in the art and even to the general public that medical science, despite decades of intense research, has not found any antigen, immunogen, or compound that can be credibly used as a vaccine against HIV.

The difficulties inherent to developing an HIV vaccine are well known. For the sake, of clarity, some of those problems are outlined here:

1) the extensive genomic diversity associated with HIV, due in large part to error prone reverse transcription of its RNA genome,
2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a covert form (cell to cell transmission), as well as via free virus transmission,
3) the existence of latent forms of the virus,
4) the complexity and variation of the elaboration of the disease, and
5) the property of some portions of HIV proteins or peptides to actually cause immunosuppression or other detrimental consequences.

The existence of these obstacles prevents one of ordinary skill in the art from accepting any therapeutic regimen on its face given the intense

interest in developing HIV treatments or vaccines and the lack of success in doing so.

Working examples. The specification contains examples showing the immunogenicity of the multi-clade "vaccine" and examples where monkeys are vaccinated with a multi-clade HIV "vaccine" and challenged with SHIV. None of the examples, however, show complete protection where there is prevention of HIV infection. There are no examples showing vaccination with a multi-clade immunogen and challenge with HIV resulting in complete protection or prevention of HIV infection.

Guidance in the specification. The claimed invention is directed to a vaccine against HIV. There is insufficient disclosure to reasonably predict that the claimed vaccine of the instant specification would prevent HIV infection. In addition, the disclosure fails to provide any guidance pertaining to the correlates of human protection. To date, it is not clear what type of immune response is required to provide a therapeutic benefit.

The disclosure also fails to provide any guidance pertaining to the development of a persistent and protective HIV-l-specific immune response. It is not readily apparent if the recited HIV vaccine will generate an HIV-l-specific immune response of sufficient magnitude and duration that long-lasting protection against HIV-1 infection and the development of AIDS would be provided.

Applicants have shown immunogenicity studies in mice, e.g., several of the "stabilized tat antigens" elicit an immune response in mice by producing anti-tat antibodies. Applicants' specification lacks experimental evidence that the disclosed immunogens can prevent HIV infection or HIV-1 transmission following the administration of said vaccine.

Predictability or unpredictability of the art. The state-of-the-art *vis-à-vis* HIV vaccine development is one of unpredictability (Haynes *et al.*, 1996; Burton and Moore, 1998; Moore and Burton, 1999; Desrosiers, R., 2004). To date, there is not one single effective HIV vaccine on the market. Several clinical trials have been conducted but in every situation, the immunogen failed to induce a long-lasting and high-titer immune response.

Accordingly, when all the aforementioned factors are considered *in toto*, it would require undue experimentation for one skilled in the art to practice the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 36 recites, in part, "said non-metal ligand in a) or in c) is protein, lipid, carbohydrate, nucleotide or mixed in nature".

It is unclear from the Specification or preceding claim what is meant by the term "mixed in nature". Is the phrase used to mean that the non-metal ligand may be a combination of protein, lipid, carbohydrate or nucleotide? The Specification recites various proteinaceous and carbohydrate ligands used to induce an immune response in mice, but it is unclear that Applicants mixed proteinaceous and carbohydrate ligands in the immunogenic preparation.

6. Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 44 recites, in part, "or fragment above". It is unclear from the context of the Claim and the examples of the Specification whether the "fragment above" is referring to the fragments in the claim, other claims or the Specification.

7. Claim 45 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 45 recites the phrase "derives from" in reference to a stabilized Tat antigen and SEQ ID No.:1. However, it is unclear from the context of the Claim and the Examples of the Specification what modifications of the listed sequence Applicants intended. Clearly most modifications other than complete proteolytic or chemical cleavage would still result in an immunogenic preparation, but other than that unrealistic example, Applicants have provided limited guidance as to the nature and extent of modification of the protein.

8. Claim 46 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

9. Claims 46, 49, 50 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 45 and 53 each recite the broad recitation “polyvalent cations”, and the claim also recites “preferably divalent

cations, such as Zn^{2+} or Cd^{2+}" which is the narrower statement of the range/limitation; claims 49, 50, and 53 each recite "oligomer" followed by "preferably a dimer".

10. Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 54 recites "that said Tat protein and/or the fragment of said protein…are in the form of a polynucleotide or a recombinant vector encoding said protein and/or said fragment". It is well known in the biochemical arts that proteins and fragments thereof are distinct from polynucleotides chemically and functionally. For example, proteases degrade proteins and peptides but have no effect on polynucleotides and with the exception of ribozymes, polynucleotides in general do not possess catalytic functions although in the case of siRNA may exert specific and profound biological effects.

11. Claim 58 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 58 provides for the use of a stabilized Tat antigen as a vaccine, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

12. Claim 58 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 35, 36, 44, and 54 are rejected under 35 U.S.C. 102(b) as being anticipated by Marasco, *et al.* The claims are drawn to a stabilized tat antigen resistant to proteolytic degradation selected from the group consisting of, inter alia, an HIV Tat protein and a non-metal ligand of Tat (claim 35); wherein the non-metal ligand is, inter alia, protein (claim 36); and Tat consists of, inter alia, 86 amino acids (claim 44); and the tat may be in the form of a polynucleotide. Marasco, *et al.* teaches a tat/intrabody composition that inherently possesses the property of proteolytic degradation resistance (see section 1 above), the intrabody consisting of a protein. Furthermore, the intrabody producing cells were infected with HIV-1_{IIIB} known to consist of 86 amino acids (see NCBI accession number P04608, attached). Finally, infection of intrabody-transduced cells

infection with the virus provided the tat portion of the complex via nucleotide, e.g., the HIV-1 genome encoding and subsequently expressing tat.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco, *et al.* as applied to claims 35, 36, 44 and 54 above, in further view of Sànchez, *et al.* The claims add the further limitation to the vaccine formulation of claim 35 that the non-metal ligand consists of, *inter alia*, heparin. Sànchez, *et al.* teaches the use of heparin as a stabilizer of protein vaccines. Use of heparin compared favorably to several other materials known to stabilize antigenic proteins; Tables 1 and 2 demonstrate that use of heparin in putative protein vaccine preparations results in ~80-90% retention of antigenicity of the protein whereas Figures 3-5 demonstrate that antigenic protein is release from heparin-stabilized proteins for up to 40 days.

It would have been obvious to include heparin in immunogenic compositions. A skilled artisan would have been motivated by the desire to retain the immunogenicity of a protein-based immunogen and would have had a reasonable expectation of success in such retention of immunogenicity in view of the teachings of Sànchez, *et al.* especially the tables and figures cited above.

Thus, it would have been *prima facie* obvious to combine teachings of the Marasco, *et al.* with those of Sànchez, *et al.* to arrive at the instant invention.

15. Claims 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marasco, *et al.* as applied to claims 35, 36, 44 and 54 above, in further view of Linblad (2004). Claims 55-57 add the limitation that the vaccine composition of either claims 35 or 55 further comprise an adjuvant (claim 55), especially aluminum hydroxide (claim 57) and/or pharmaceutically acceptable vehicle and/or a carrier substance. Linblad reviews the history of aluminum based compounds and restates the common and long held knowledge that vaccines often comprise aluminum-based adjuvants because of the long safety history and profile. Furthermore, the USDA and FDA approved vaccines listed in Linblad (see page 3662, table 1) each are formulated in pharmaceutically acceptable vehicles, especially sterile, pyrogen free water or PBS. Thus, Linblad, *et al.* teaches each and every limitation of claims 55-57 not taught by Marasco, *et al.* It would have been obvious to combine the teachings of Marasco, *et al.* and Linblad to arrive at the instantly claimed invention of claims 55-57. A skilled artisan would have been motivated to include aluminum-based adjuvant and pharmaceutically and pharmaceutically acceptable carriers in the composition of Marasco, *et al.* because of the desire to increase the immune response of the immunogen, the long safety record of aluminum-based adjuvants and, in the case of pharmaceutically acceptable carrier, the desire to safely administer the vaccine explicitly and implicitly taught by Linblad. Furthermore, a skilled artisan

would have a reasonable expectation of success in combining the two compositions because of the effectiveness of aluminum-based adjuvants in increasing the immunogenicity of a wide variety of immunogens (see Linblad, page 3662, table 1). Thus, it would be *prima facie* obvious to formulate a stabilized tat composition with an aluminum-based adjuvant in a pharmaceutically acceptable carrier as required by the limitations of claims 55-57.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to STUART W. SNYDER whose telephone number is (571)272-9945. The examiner can normally be reached on 9:00 AM-5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce R. Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mary E Mosher/
Primary Examiner, Art Unit 1648

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Examiner
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sws